REMARKS

Status of the Claims

Claims 1-19 are pending in this application. Claims 5 and 8-19 are withdrawn from consideration. Claims 1, 6, and 7 are amended herein. No new matter is entered by these amendments. Claim 4 is cancelled herein without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in one or more continuation or divisional applications. Claims 1-4, 6, and 7 have been rejected by the Examiner.

Claim Objections

Claims 4, 6 and 7 are objected to for informalities, as indicated by the Examiner. Claim 4 is cancelled herein, and therefore the objection is moot. Applicants thank the Examiner for pointing out the misspellings in claims 6 and 7, and have amended claims 6 and 7 to correct those misspellings as suggested by the Examiner. Accordingly, Applicants submit that they have addressed the Examiner's objections to the claims.

Claim Rejections

35 U.S.C. §102(b)

Claims 1-4, 6 and 7 continue to stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Schenk et al. (WO 00/72880; "Schenk"). Applicants respectfully traverse this rejection for the reasons set forth below.

As the Examiner is aware, a claim is only anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, (Fed. Cir. 1987). Schenk fails to teach each element of the instant claims, and as such does not anticipate the instant claims. The instant claims are directed to a method of treatment of a patient of a disease, which treatment method comprises administering to a patient in need thereof an effective amount of an Aβ peptide conjugated to a protein immunogen in which the peptide induces production of antibodies that (1) specifically recognize any of the predominant variants of a beta amyloid Aβ40

or Aβ42 peptide and (2) effectively reduce amyloid deposition in the patient. As amended herein, claim 1 and its dependents all now specify that the peptide is either SEQ ID NO: 2 (Aβ33-40) or SEQ ID NO:3 (Aβ33-42) or a peptide resulting from lengthening the peptide by an additional amino acid residue appropriate for conjugating the protein to the peptide of SEQ ID NO: 2 or SEQ ID NO: 3.

Schenk, on the other hand, teaches use of Aβ1-42 and fragments and conjugates thereof as immunogens to raise an immune response against Aβ and APP in order to treat diseases associated with amyloid deposits of Aβ. When Schenk does call out specific Aβ peptides for use in methods of treating diseases associated with amyloid deposits, it specifies N-terminal Aβ peptides containing at least Aβ1-5 or beginning at residue Aβ1-3 and ending at residue Aβ7-11, and, in some embodiments, a peptide that does not induce an immune response against an epitope within residues Aβ12-43 (specification at page 4, lines 5-19). That is, when Schenk teaches specific Aβ peptides, it teaches peptides from the N-terminal portion of Aβ, while SEQ ID NOS:2 and 3 are from the C-terminal portion of Aβ.

As the Examiner recognizes, Schenk does have examples in which Aβ33-42 (SEQ ID NO:3) is tested. In particular, Schenk administers a variety of Aβ peptides, conjugates and aggregates, including Aβ33-42 conjugated via a cysteine to a sheep-anti-mouse IgG, to PDAPP transgenic mice to assess the ability of these peptides to induce an immune response and to reduce amyloid levels in the transgenic mouse. The peptides, including Aβ33-42, all appeared able to induce antibodies against Aβ. However, while certain of the peptides, specifically aggregated human Aβ1-42, rodent Aβ1-42 conjugate, and the Aβ1-5 conjugate, had activity to reduce amyloid levels in the cortex of the transgenic mice (only the aggregated human Aβ1-42 reduced amyloid levels in the hippocampus), the administration of Aβ33-42 to mice was shown not to be effective to reduce amyloid levels (specification at p. 64, line 30 to page 65, line 2). In addition, Schenk tests the ability of lymphocytes from transgenic mice administered the Aβ33-42 peptide to proliferate in response to exposure to Aβ *in vitro*, which, according to Table 5 (page 67), they do not.

Accordingly, Schenk does not disclose each and every limitation of the rejected claims. Schenk does not teach a method of treating humans with disease using the Aβ33-42 or Aβ33-40

peptides that induces antibodies against Aβ effective to reduce amyloid levels. The administration of Aβ33-42 in PDAPP transgenic mice reportedly did not result in reduction in amyloid levels in either the cortex or the hippocampus. Thus, Schenk does not disclose a method of administration that includes each and every element of the claims because the method is not effective to reduce amyloid levels that would be required to treat disease. The other methods disclosed by Schenk that involve administration of Aβ33-42 likewise do not fall within the claim—neither assessing induction of antibody production in mice nor *in vitro* testing of a lymphoproliferative response in cells from mice administered the Aβ33-42 peptide constitute treating any disease condition. Accordingly, Schenk does not disclose a method of treatment with the SEQ ID NO:2 or SEQ ID NO:3 peptides resulting in induction of antibodies that reduce amyloid accumulation, as required in the instant claims.

Also, Schenk does not teach a method of treatment of a "patient" with an Aβ33-42 or Aβ33-40 conjugated peptide. Schenk only administers Aβ33-42 to PDAPP transgenic mice. Such transgenic mice are not "patients," as is made clear by a review of the specification. The instant specification briefly describes prior published experimental work done with Aβ (see page 2, lines 1-18). In characterizing these experiments, the specification describes human subjects receiving the Aβ as "patients." For example, the specification characterizes as "patients" the subjects of the examples in EP526511 in which Aβ is administered to human subjects and the subjects of a phase III clinical trial, which necessarily involves human subjects. In the same passage, when describing experiments very similar to those disclosed in Schenk using PDAPP transgenic mice, the specification characterizes the subjects as "transgenic mice" and not "patients." Thus, in view of the specification, one skilled in the art would understand that "patients" means human subjects in need of treatment for an amyloid related disease, such as Alzheimer 's disease, and NOT transgenic mice. As Schenk only discloses administration of the Aβ33-42 peptide to transgenic mice, Schenk does not disclose administration of either SEQ ID NO:2 or 3 to a "patient" as required by the claim.

In sum, Schenk does not disclose each and every element of the claim because it does not disclose a method of treatment with Aβ33-40 or Aβ33-42 (SEQ ID NOS:2 and 3, respectively) conjugated with a protein immunogen, and does not disclose a method using these peptide

conjugates in a patient. Thus, the cited references do not anticipate any of the pending claims. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(b).

35 U.S.C. §102(e)

Claims 1-4 continue to stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Yednock et al. (U.S. published application 2006/0188512; "Yednock"). Applicants respectfully traverse the rejection, and assert that Yednock does not anticipate Applicants' claims. As discussed above, the claims have been amended such that claim 1 recites "wherein the peptide is selected from the group consisting of the peptide of SEQ ID NO: 2, the peptide of SEQ ID NO: 3, and a peptide resulting from lengthening by an additional amino acid residue appropriate for conjugating the protein to the peptide of SEQ ID NO: 2 or SEQ ID NO: 3." Yednock does not teach these specific peptides, much less their use in a method of treatment as recited in the pending claims. Yednock, thus, does not teach at least the quoted elements of the claims, i.e., and therefore does not anticipate the claims.

For at least the foregoing reasons, Yednock does not anticipate Applicants' claims, and Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(e).

Rejection Under 35 U.S.C. §103(a)

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. §103(a) as being obvious over Chain, (US 2003/0073655; "Chain"). Applicants respectfully traverse this rejection.

Any finding of obviousness requires that there be a reasonable expectation of success (see MPEP § 2143.02(I) ("The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success.")). Absolute predictability is not required for obviousness, but at least some degree of predictability is required for there to be a reasonable expectation of success (see MPEP § 2143.02(I); In re Merck & Co., Inc., 800 F.2d 1091 (Fed. Cir. 1986)). It is against this legal background that Applicants' claims must be examined. The Examiner has failed to make out a *prima facie* case of obviousness, because Chain fails to provide one of ordinary skill in the art with a reasonable expectation of successfully performing Applicants' invention.

Chain is directed to treating Alzheimer's disease by administering antibodies that have been obtained by immunizing an animal with Aβ peptides resulting in antibodies specific for Aβ. The Examiner conclusively states that based on Chain's "disclosed therapeutic method of passive immunization comprising administration of antibodies, "it would have been obvious to the ordinarily skilled artisan to use a specific peptide immunogen conjugate to elicit a specific antibody response for therapy of AD" (see Office Action at p. 9).

The Examiner, however, provides no evidence or specific reasons whatsoever to support this contention, and instead simply states: "This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results" (see Office Action at p. 9). That a skilled artisan may be aware of various "options" or strategies within a given field does not somehow make the application of those options a predictable pursuit.

In particular, Chain, taken alone, or combined with any of the other art cited by the Examiner, would not have provided one of ordinary skill in the art with a reasonable expectation of successfully treating a disease characterized by the accumulation of amyloid deposits in the brain of a patient comprising administering to the patient an effective amount of the peptides recited in Applicants' claims, conjugated to a protein immunogen to produce the antibodies as specified in Applicants' claims. Chain does not exemplify antibodies produced using or specific for the peptides of SEQ ID NO:2 or SEQ ID NO:3. The antibodies in the examples in Chain are produced using Aβ1-5 (Chain at paragraph 104), and Chain does not show any evidence of efficacy even for these antibodies at reducing amyloid deposits. Thus, even if Chain did make active immunization obvious, which it does not, Chain certainly does not make obvious, i.e., does not provide a reasonable expectation of success for, active immunization with the recited peptides.

Further supporting that Applicants' claims are not rendered obvious by Chain, the art, including other art relied on by the Examiner in the instant Office Action, actually teaches away from Applicants' claimed invention. For example, Schenk, which was cited by the Examiner in rejections discussed above, teaches that Aβ33-42 would not serve as an appropriate immunogen. Schenk explains that "certain epitopes within residues 10-18, 16-24, 18-21, and 33-42 lack

activity," and that therefore "[i]t is recommended that such antibodies be screened for activity in the mouse model described in the Examples before use" (see Schenk, p. 18-19; emphasis added).

As discussed above with respect to the rejection over Schenk, Schenk tested Aβ peptides, including Aβ33-42, in transgenic mice and determined that the Aβ33-42 peptide was not effective to reduce amyloid levels in the cortex or hippocampus of the mice (see Schenk, pp 64-65). Thus, one of ordinary skill in the art would, in view of Schenk, have been dissuaded from choosing, out of the numerous portions of Aβ described in Chain as immunogens for antibodies for passive immunotherapy, the Aβ33-42 peptide for use as a conjugate in active immunotherapy, which the Examiner admits is not taught by Chain, to treat diseases characterized by amyloid deposits.

Schenk provides further evidence of teaching away from using the recited peptides in the claimed methods of treatment in results reported for activity of anti-Aβ antibodies. Schenk discloses that antibody 21F12 has specificity for the epitope Aβ33-42 (see Schenk at p. 69, Table 6), and the data provided in Table 16, which represent an analysis of epitope specificity, show that antibodies binding to epitopes C-terminal to residue 10, which include Aβ33-42, "neither bind nor clear amyloid deposits" (see p. 96-97). These data are confirmed in Schenk by studies that tested and compared the ability of various antibodies against Aβ to induce phagocytosis in an *ex vivo* assay, and their ability to reduce *in vivo* plaque burden in passive transfer studies. Table 17 shows that "[a]lthough 16C11 and 21F12 bound to aggregated synthetic Aβ peptide with high avidity, these antibodies were unable to react with β-amyloid plaques in unfixed brain sections, could not trigger phagocytosis in the *ex vivo* assay, and were not efficacious *in vivo*." These data suggest that passive immunization with an antibody that binds the Aβ33-42 peptide would not be effective, and, thus, teaches an ordinarily skilled artisan away from using the Aβ33-42 peptide for active immunization. It is clear, therefore, that the prior art teaches away from Applicants' claimed invention.

With respect to Chain, the teachings away in Schenk provide further support for the fact that disclosure of passive immunization with Aβ peptides does not provide any reasonable expectation that actually carrying out the specific methods of the claims using Aβ peptides not tested in Chain would be successful.

For at least the foregoing reasons, Applicants assert that Chain does not render Applicants' claims obvious. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejections, and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 05-1323, Docket No. 105090.61194US. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 05-1323, Docket No. 105090.61194US.

Respectfully submitted,

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